Description

Implant with antibiotic long-term action

5   [0001] The invention relates to an implant with
antibiotic   long-term   action.   Infection   following
implantation of prostheses and other implants is a risk
factor feared by physicians and patients alike. The
incidence of implant infection is approximately 0.5 to
10   5%. Risk factors affecting artificial vascular implants
are, for example, emergency operations, a subcutaneous
position of the prosthesis or, possibly, positioning of
the prosthesis in the inguinal region. A distinction is
drawn between early infections, which generally occur
15   within a period of up to 4 months after implantation,
and so-called late infections which become apparent
after a longer period of time has elapsed since
implantation. Clinical reports confirm, for infections
of the aorta for example, an onset after 25 - 70
20   months. In the aorto-femoral position, the average time
until onset of infection is 41 months. Extracavitary
prosthesis infections occur earlier (within 7 months).
The microbes which cause such infections include, in
particular,   Staphylococcus   aureus,   Staphylococcus
25   epidermidis   and   Escherichia   coli.   The   infection
generally results from intraoperative contamination.
However, it can also occur in the post-operative phase,
in particular in the case where the patient has an
infection that has not completely healed. The microbes
30   or microorganisms tend to adhere to the prosthesis
surface. In doing so, they may form a microcolony
within a biofilm, and in the course of time they may
become sealed off from the outside. Particularly in
cases where the patient has been weakened for other
35   reasons, virulent infection and inflammatory reactions
may occur with involvement of the perigraft tissue and
the anastomosis regions.

[0002] It is known that silver has an antibiotic action. Silver salts and metallic silver are therefore widely used to combat microorganisms. Thus, it is known, for example from WO 93/07924, for articles made
5 of plastics, metal and ceramics and introduced into the body, for example fixation devices, nails, pins, catheters, stents, tracheostomy tubes, shunts, percutaneous connectors, wound drainage devices, dental implants and the like, to be provided with a
10 bactericidal component, in particular of platinum, iridium, gold, silver, mercury, copper, iodine and their alloys, compounds and oxides. The corresponding substances are applied in the form of ionized atoms in a vacuum chamber by ion-beam-assisted deposition
15 (IBAD). Biomedical implants with similar bactericidal surfaces are described in US 5,492,763. In the latter, biomedical articles such as metallic needles, urology catheters, percutaneous clamps and ceramic and metallic countersurfaces of hip joints and knee joints are
20 mentioned.

[0003] From WO 81/02667, it is also known to provide implants, for example artificial joints, with a surface coating of silver or silver alloys in a layer thickness
25 of 25 to 500 Å, in order, on the one hand, to avoid bacterial growth and, on the other hand, to ensure that the amount of silver is not so great as to damage surrounding connective tissue.

30 [0004] From US 5,464,438 it is also known for metallic gold to be vapor-deposited on implants made of textile material, in order to reduce the risk of thrombosis.

[0005] Textile implants, especially when used as
35 replacements for hollow organs, in particular ducts, and chiefly including vascular prostheses, are normally provided with sealing coatings in order to close the pores of the textile prostheses at least initially. It

has been proposed to incorporate bactericidal
substances into the coating material in order in this
way to be able to avoid infections after implantation.
Such coatings, which among other things can contain
5   silver ions, are set out in WO 00/32247.

[0006] It is an object of the invention to make
available an implant, in particular a vascular
prosthesis, with antibiotic long-term action, which
10   implant is to be able to be handled in the normal way
and will reduce the risk of infection to a minimum.

[0007] The subject of the invention is an implant with
antibiotic or antimicrobial long-term action, in
15   particular a vascular prosthesis, with a basic
structure which defines the form of the implant and
which is made of substantially non-absorbable or only
slowly absorbable polymer material and of a coating of
an absorbable material, with a layer of metallic silver
20   situated on the polymer material and underneath the
coating.

[0008] It was to be feared that an interaction would
take place between the absorbable coating and the
25   silver layer. This is also actually the case especially
when the absorbable layer is made of biological
material such as gelatin and collagen. However, it was
found that this interaction is rather of advantage.
Thus, as will be explained in more detail below,
30   comparative tests have shown that the release of silver
ions in prostheses provided with an absorbable layer is
initially very high compared to prostheses provided
only with a silver layer, even when no silver was
incorporated in the absorbable layer. The silver layer
35   is evidently corroded by the constituents of the
absorbable layer, which can occur during storage of the
prosthesis up to the time it is used. Released silver
ions deposit in the absorbable layer and, as the latter

breaks down, are released more rapidly. If the silver
layer is of sufficient dimension, this does not impair
the long-term action of the silver layer, with the
result that the bactericidal action of the silver layer
5 is maintained for a long time even when the absorbable
layer is broken up.

[0009] The silver layer advantageously adheres firmly
to the surface of the polymer material and is in
10 particular anchored in it. This can be achieved using
the vapor-deposition methods known from the prior art,
in particular the abovementioned IBAD technique. The
silver layer is therefore preferably vapor-deposited
onto the polymer surface. It is particularly preferred
15 if the silver atoms of the silver layer are impressed
into the polymer surface of the basic structure. This
can advantageously be done by bombarding the polymer
surface with argon ions, for example, during the vapor-
deposition.

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[0010] The silver layer covers the polymer surface at
least at the locations where it comes into contact with
connective tissue after implantation, and it preferably
covers it completely. Closed silver layers are present
25 in particular at least in these areas. In the preferred
embodiment, the silver layer is of such thickness that
in vivo, i.e. after implantation, it has a dwell time
on the polymer surface of more than one year, in
particular of more than 2 years, and releases silver
30 ions during this time. It is particularly advantageous
if the silver layer is of such thickness that, as it
breaks down in the body, only about 5 to 10%, in
particular 7 to 8%, of the layer thickness is removed
per annum. It has in fact been found that the possible
35 damage to the surrounding tissue, as described in the
literature, is not a function of the layer thickness of
the silver layer. Thicker layers do not release more
silver ions per unit of time, but as a result they

release them for a longer period of time. Layer
thickness in the range of 1000 Å to 2500 Å have
proven useful, in particular those of ca. 1300 Å. Such
layer thicknesses exhibit a good long-term action. The
5   layer thickness can also be greater and amount to as
much as 4000 Å and over, but greater layer thicknesses
do not bring any real additional advantages. Smaller
layer thicknesses may, particularly because of the
interaction with the absorbable layer, lead to an
10 undesirably early attenuation of the long-term action.

[0011] The polymer material for the basic structure
can be from the usual polymers used in implants, in
particular vascular prostheses, for example polyester,
15 polytetrafluoroethylene, polyurethane and, in special
cases, also polyamides, preference generally being
given to polyester. The silver layer is preferably
situated at least on the side or sides of the polymer
material facing toward the connective tissue. The
20 silver layer is preferably composed of pure elemental
silver.

[0012] The basic structure of the implant is porous,
especially in the case of a vascular prosthesis, but
25 also in the case of hernia meshes, patches and the
like, and the absorbable layer is an impregnation which
seals off the pores of the implant. As has already been
mentioned above, the absorbable layer can be formed
from biological material which, if appropriate, can be
30 crosslinked. Possible materials are, in particular,
collagen, gelatin and albumin. Alternatively, or in
combination, the absorbable layer can also be made from
synthetic polymers and copolymers which are degradable
or absorbable *in vivo*. In addition to at least
35 partially water-soluble polymers such as polyvinyl
alcohol and carboxymethylcellulose, these mainly
include the polymers and copolymers of hydroxy acids.
In this context, these are in particular polymers and

copolymers of glycolide, lactide, ε-caprolactone,
trimethylcarbonate and paradioxanone. It is also
possible to use mixtures of the polymers. By suitable
choice of the polymers, the desired duration of
5 absorption can be set. This is preferably within 4
months and in particular within 40 days. Such a time is
expedient since, depending on the type of prosthesis,
the impregnating action is no longer necessary during
this time because of the ingrowing connective tissue.

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[0013] The coating of absorbable material, which in
the case of a flat implant can be provided on just one
side or else on both sides and can also be made of
different materials depending on the intended
15 application, can in turn contain active substances
which are released into the surroundings during the
absorption period. These are mainly active substances
other than silver, for example antibiotics with a
particular spectrum of action, or growth factors,
20 active substances with hormonal action, and so on.

[0014] A porous basic structure is particularly
advantageously made from a textile material, as is the
case for example in vascular prostheses and hernia
25 meshes. Suitable materials are formed-loop knits,
drawn-loop knits, braids, wovens and nonwovens,
preference usually being given to formed-loop knits. It
is also possible to use combinations of the textile
structures, for example formed-loop knits which have a
30 nonwoven cover layer. Porous sintered material, such as
expanded polytetrafluororethylene, can also be used as
polymer material, and this is a frequently used polymer
material especially for vascular prostheses.

35 [0015] The silver layer is preferably a closed silver
layer. However, this does not mean that the pores in
the case of a porous vascular structure are sealed off
by the silver layer. Rather, the silver layer adapts to

the surface structure of the polymer material so that
the pores retain their original shape and size. This
applies for expanded polytetrafluoroethylene in the
same way as for textile fiber material. In the case of
5   fiber material, the fiber surface is coated with
silver. In the case of textile fiber material, it is
possible to provide the fibers or yarns with the silver
layer before the basic structure is formed from them.
It suffices, however, for silver to be vapor-deposited
10 onto the finished basic structure at the accessible
and/or desired locations, since it is these locations
which are exposed to the risk of infection and come
into contact with the surrounding tissue.

15 [0016] Further features of the invention will be
evident from the following description of preferred
embodiments in conjunction with the dependent claims.
The individual features of one embodiment can in each
case be realized singly or severally.

20

[0017] Example 1

[0018] Double-velour knitted prostheses of polyester
are clamped in a rotatable clamp device so that they
25 hang freely as a bundle of parallel tubes with spaces
between them. The clamp device is introduced into a
vacuum chamber suitable for carrying out the IBAD
technique, the vascular prostheses being vapor-
deposited with silver and at the same time bombarded
30 with argon ions. The coating operation is conducted
until a silver layer thickness of 1300 Å is reached on
the outside of the vascular prostheses or the fibers
located there. If so desired, a primary coating can be
effected by vapor-deposition of other metals. Silver is
35 also forced into the pores or interstices between the
fibers of the vascular prostheses, so that the fiber
surfaces are coated at these locations too. However,
the layer thickness is less there because of the

"shadow effect" in the vapor-deposition.

[0019] The vascular prostheses coated in this way are removed from the clamp device and then impregnated in the usual manner with absorbable material at least on their outside, sealing off the porous structure. This impregnation can be done in the usual way with collagen, in which partial crosslinking with glutaraldehyde is effected. Preference is given to a likewise known coating with gelatin which is crosslinked with diisocyanate. As has been mentioned, bioactive substances can be introduced into the coating solution in order to develop the biological activity during the later absorption of the layer.

[0020] Determination of the amount of silver on the vascular prostheses (still without absorbable layer) has revealed that the proportion of silver relative to the total weight of the metallized prosthesis lies in the range of from 0.4 to 0.8% by weight. The proportion of silver depends inter alia on the porosity of the basic structure of the vascular prosthesis. Close-knitted structures have a lower percentage proportion of silver than more porous structures. Moreover, the penetration of the porous implant with silver can be influenced by the way in which the method is carried out, for example by moving the implants during vapor-deposition, by guiding the streams of vapor and gas in a particular way, etc. If, for example, an inner coating of tubular prostheses with silver is also desired, silver vapor can also flow through the inside of the prostheses during the coating operation. Turning the prosthesis round prior to a repeated vapor-deposition also leads to an inner coating.

[0021] Comparison test

[0022] A vascular prosthesis according to Example 1,

but not yet provided with the absorbable impregnation layer, was placed in phosphate buffer (pH 7.4) at 37°C; the phosphate buffer was changed daily and the silver content in the previous phosphate buffer sample was determined. The test extended across a period of 365 days. The silver content in the removed phosphate buffer was initially 35 microgram/l and then fell rapidly, and then after 50 days slowly (15 microgram/l), and after 365 days it was ca. 5 microgram/l.

[0023] Under the same conditions, a vascular prosthesis according to Example 1 was examined which was coated with an absorbable impregnation layer of gelatin crosslinked with diisocyanate. Although no silver was added to the gelatin, a high content of silver in the range of ca. 70 to 80 microgram/l was initially found in the phosphate buffer, and although it decreased slightly it remained high until the absorbable layer had largely broken up. It was not until after about 50 days that the silver content in the phosphate buffer had fallen to the level shown after 50 days by the vascular prosthesis not provided with the impregnation coating, after which time the release of the silver ions into the phosphate buffer was essentially the same as in the vascular prosthesis without impregnation coating.

[0024] This comparison shows that the silver layer was attacked via the impregnation coating, and silver ions were released into the impregnation coating, and these then entered the phosphate buffer at an increased rate and in increased number. The vascular prosthesis provided with the impregnation layer thereafter showed a comparable release of silver ions, which means that the initial strong release of silver has no negative effect on the long-term action.

Tissue reaction

[0025] Vascular prostheses produced in a similar way,
but with silver layers of 1600 Å and 2500 Å, were
5   implanted in rats, rabbits and pigs. Upon explantation
after 3 months and 6 months, good integration was
found. All the implants showed no abnormal findings.
The internal organs too showed no abnormal findings.
There were no signs of chronic inflammatory reactions.
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Artificial infection

[0026] A comparison was conducted using implants
according to the invention, and implants which, instead
15   of having a silver layer on the basic structure,
contained silver acetate incorporated in the absorbable
coating. The comparison specimens were artificially
infected with problem microbes and implanted in
rabbits. They were explanted after 7 days. The
20   comparison specimens were then incubated for 48 hours
in CASO broth, after which a microbial count was
conducted. The microbial colonization was determined
microbiologically in 36 specimens. It was found that,
in the implants according to the invention, only 22%,
25   i.e. 8 implants, were colonized with a small number of
microbes, whereas, in the implants with silver acetate
in the absorbable coating, infection was found in 67%,
corresponding to 23 implants.